Safety of dabigatran etexilate for the secondary prevention of venous thromboembolism in children

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This open-label, single-arm, prospective cohort trial is the first phase 3 safety study to describe outcomes in children treated with dabigatran etexilate for secondary venous thromboembolism (VTE) prevention. Eligible children aged 12 to <18 years (age stratum 1), 2 to <12 years (stratum 2), and >3 months to <2 years (stratum 3) had an objectively confirmed diagnosis of VTE treated with standard of care (SOC) for {greater than or equal to}3 months, or had completed dabigatran or SOC treatment in the DIVERSITY trial (NCT01895777) and had an unresolved clinical thrombosis risk factor requiring further anticoagulation. Children received dabigatran for up to 12 months, or less if the identified VTE clinical risk factor resolved. Primary endpoints included VTE recurrence, bleeding events, and mortality at 6 and 12 months. Overall, 203 children received dabigatran, with median exposure being 36.3 (range 0-57) weeks; 171/203 (84.2%) and 32/203 (15.8%) took capsules and pellets, respectively. Overall, 2/203 (1.0%) children experienced on-treatment VTE recurrence, and 3/203 (1.5%) experienced major bleeding events, with 2 (1.0%) reporting clinically relevant non-major bleeding events, and 37 (18.2%) minor bleeding events. There were no on-treatment deaths. On-treatment postthrombotic syndrome was reported for 2/162 (1.2%) children who had deep vein thrombosis or central line thrombosis as their most recent VTE. Pharmacokinetic/pharmacodynamic relationships of dabigatran were similar to those in adult VTE patients. In summary, dabigatran showed a favorable safety profile for secondary VTE prevention in children aged from >3 months to <18 years with persistent VTE risk factor(s).

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Clinical trial registration information (if any): 1160.108 ClinicalTrials.gov number NCT02197416

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Suggested short title: Dabigatran secondary VTE prevention in children

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Key Points

- Few children developed recurrent VTE using dabigatran pediatric formulations as secondary VTE prophylaxis.
- Few children experienced major or clinically relevant non-major bleeding events when receiving secondary VTE prophylaxis with dabigatran.

Abstract

This open-label, single-arm, prospective cohort trial is the first phase 3 safety study to describe outcomes in children treated with dabigatran etexilate for secondary venous thromboembolism (VTE) prevention. Eligible children aged 12 to <18 years (age stratum 1), 2 to <12 years (stratum 2), and >3 months to <2 years (stratum 3) had an objectively confirmed diagnosis of VTE treated with standard of care (SOC) for ≥3 months, or had completed dabigatran or SOC treatment in the DIVERSITY trial (NCT01895777) and had an unresolved clinical thrombosis risk factor requiring further anticoagulation. Children received dabigatran for up to 12 months, or less if the identified VTE clinical risk factor resolved. Primary endpoints included VTE recurrence, bleeding events, and mortality at 6 and 12 months. Overall, 203 children received dabigatran, with median exposure being 36.3 (range 0-57) weeks; 171/203 (84.2%) and 32/203 (15.8%) took capsules and pellets, respectively. Overall, 2/203 (1.0%) children experienced on-treatment VTE recurrence, and 3/203 (1.5%) experienced major bleeding events, with 2 (1.0%) reporting clinically relevant non-major bleeding events, and 37 (18.2%) minor bleeding events. There were no on-treatment deaths. On-treatment postthrombotic syndrome was reported for 2/162 (1.2%) children who had deep vein thrombosis or central line thrombosis as their most recent VTE. Pharmacokinetic/pharmacodynamic relationships of dabigatran were similar to those in adult VTE patients. In summary, dabigatran showed a favorable safety profile for secondary VTE prevention in children aged from >3 months to <18 years with persistent VTE risk factor(s).

(Funded by Boehringer Ingelheim; 1160.108, ClinicalTrials.gov identifier, NCT02197416)

Introduction

Venous thromboembolism (VTE) in children is associated with considerable morbidity and mortality.[1-4] Preventing secondary VTE in children poses a challenge for clinicians, due to the evolving maturation of a child's hemostatic system with age, which affects not only the risk of recurrent VTE but also the pharmacokinetics and responses to anticoagulants and antiplatelet therapies.[5,6] Risk factors for recurrent VTE, the presence of comorbidities, failure to monitor VTE adequately to inform treatment decisions, and limited vascular access (which may impact treatment choice) contribute to treatment complexity.[5,6] Risk factors that have been reported to be associated with recurrent VTE in children include central venous access devices, infection, cancer, congenital heart disease, and thrombophilia.[1,7,8]

Current standard of care (SOC) for the secondary prevention of VTE in children, including low molecular weight heparins (LMWH) or oral vitamin K antagonists (VKA), depends primarily upon the cause and risk factors of the first VTE event, with recurrent VTE contributing to the severity and duration of anticoagulation.[6] However, current SOC has several limitations depending upon the anticoagulant used. For example, LMWH requires parenteral administration, whereas VKA may result in variable effects and low time in therapeutic range due to frequent food- and drug-drug interactions, requiring the need for regular laboratory monitoring to ensure dosing appropriateness of anticoagulation. Moreover, the rarity of pediatric VTE leads to difficulties in designing and managing clinical trials in this setting.[9] The treatment of VTE in children is extrapolated from evidence-based recommendations derived from studies performed in adult populations.[6] However, the hemostatic system in infants and children is profoundly different from adults. As such, pediatric safety studies are recommended by both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA).[10,11]

Some of the limitations with SOC in children with VTE could be overcome by dabigatran, a direct, oral thrombin inhibitor shown to be effective for the treatment and secondary

prevention of VTE in adults.[12-14] In addition, previous pediatric phase 2 dabigatran VTE trials have reported similar safety and pharmacokinetic/pharmacodynamic relationships to those seen in adults.[15-17] In this open-label, phase 3 trial, we report the first safety data on dabigatran etexilate for the secondary prevention of VTE in children aged <18 years, as well as the appropriateness of an age- and bodyweight-adjusted dosing algorithm for dabigatran in this setting.

Materials and methods

Trial design

The trial design has been described in detail previously.[18] In brief, this open-label, single-arm, safety prospective cohort, phase 3 clinical trial (NCT02197416) (supplemental Figure 1) is part of a Pediatric Investigational Plan agreed with the EMA Pediatric Committee, and a postmarketing requirement agreed with the US FDA. The main objective was to assess the safety of dabigatran etexilate for secondary prevention of venous thromboembolism; all study outcomes were considered safety related. The current analysis includes the data set and target enrollment[18] that fulfills the requirements of the EU Pediatric Investigational Plan agreed with the EMA Pediatric Committee, while recruitment continued in order to fulfill additional US FDA requirements. The trial was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice, and was approved by all investigational site ethics committees. Written informed consent from parents or legal guardians and pediatric patients (if they were of legal age, or if they reached legal age during the trial) was obtained before participation, according to the International Conference on Harmonisation Good Clinical Practice, and the regulatory and legal requirements of each participating country.

The trial was sponsored by Boehringer Ingelheim. Listings of trial committees and investigators are provided in the online supplement. The steering committee and sponsor

representatives developed the protocol, supervised the trial, and oversaw any required protocol amendments. The external independent data monitoring committee (consisting of the same members as for the DIVERSITY trial [NCT01895777]) regularly reviewed safety and efficacy data, advising the sponsor on whether the trial should continue, or be modified or terminated. An independent blinded adjudication committee evaluated all co-primary endpoints to confirm or refute outcome events. Boehringer Ingelheim coordinated the trial execution, and oversaw the collection, management, and analysis of trial data.

Trial population

Children aged <18 years (stratified by age: stratum 1, 12 to <18 years; stratum 2, 2 to <12 years; stratum 3, >3 months to <2 years) were eligible if they had an objectively confirmed diagnosis of VTE (eg, by compression ultrasound, computerized tomography, or magnetic resonance imaging scans) treated with SOC for ≥3 months, or if they had completed dabigatran or SOC treatment in the DIVERSITY trial and had an unresolved clinical thrombosis risk factor requiring further anticoagulation. Complete inclusion and exclusion criteria are provided in supplemental Table 1.

Treatment

Patients were treated with open-label dabigatran for up to 12 months, or less if the identified clinical risk factor for VTE resolved. An age- and weight-adjusted nomogram according to Hayton,[19] derived from estimated renal function, was used in order to dose dabigatran and achieve comparable exposure to adult populations treated with dabigatran.[18] Only one dabigatran dose modification (up- or down-titration) according to the nomogram was allowed. Different formulations of dabigatran were administered depending upon the age of the child; capsules were given to those aged 8 to <18 years, pellets to those aged <8 years (or those aged 8 to <12 years unable to swallow capsules); oral solution was offered for those aged from >3 months to <12 months who were unable to swallow pellets (but

ultimately no patient in this trial required oral solution). All patients discontinued dabigatran at the end of their trial participation and were switched to SOC if there was a continued need for anticoagulation. After completing trial treatment, patients were followed up for a period of 28 days. Patients who discontinued trial treatment prematurely were to be followed up according to the remaining visit schedule until the end of the trial or at least for 28 days. Therefore, patients who discontinued trial treatment prematurely and had a follow-up period of at least 28 days were not considered as premature trial discontinuations. Patients who completed trial treatment as planned, but did not have a follow-up period of at least 28 days, were considered premature trial discontinuations but not premature treatment discontinuations. Patients who discontinued trial treatment due to resolution of the underlying risk factor were not considered premature treatment discontinuations.

Outcomes

According to the objectives of the study, all outcomes were considered safety related. Primary endpoints were: recurrence of VTE assessed at 6 and 12 months postenrollment (defined as all recurrent VTE—contiguous progression or noncontiguous new thrombus, including deep vein thrombosis, pulmonary embolism, and paradoxical embolism confirmed by imaging); mortality (overall and thrombotic/thromboembolic event mortality) at 6 and 12 months; major bleeding events (MBEs) at 6 and 12 months (defined as: fatal bleeding; clinically overt bleeding [≥20 g/L decrease in hemoglobin over 24-hours]; retroperitoneal, pulmonary, or bleeding that involves the central nervous system; or bleeding that requires surgical intervention in an operating suite); clinically relevant nonMBEs (CRNMBEs) at 6 and 12 months (defined as: overt bleeding that is not directly attributable to the patient's underlying medical condition and requires administration of a blood product, or bleeding that requires medical or surgical intervention other than in an operating suite to restore hemostasis); minor bleeding events at 6 and 12 months (defined as any overt or

macroscopic evidence of bleeding that does not fulfill the MBE or CRNMBE criteria); and overall mortality and thrombotic/thromboembolism-related mortality.[20]

Secondary endpoints included: the occurrence of newly diagnosed or worsening of baseline postthrombotic syndrome (PTS; as per the modified Villalta scale[21,22]) at 6 and 12 months postenrollment; the relationship between plasma dabigatran concentrations (total plasma dabigatran trough levels measured at a central laboratory [Nuvisan GmbH, Neu-Ulm, Germany] by a validated high-performance liquid chromatography–tandem mass spectrometry assay) and pharmacodynamic markers (diluted thrombin time [dTT], activated partial thromboplastin time [aPTT], and ecarin clotting time [ECT] evaluated at a central laboratory [Menal GmbH, Emmendingen, Germany]); the number of patients with dose adjustments, and the acceptability of the administered formulations. The residual effect period for which events were still considered on-treatment following the last intake of trial medication was 3 days.

Statistical analysis

Boehringer Ingelheim were responsible for data collection and statistical analysis, and all authors had access to trial data. Based upon an estimated 5% event rate for the composite of recurrent VTE, major bleeds, and mortality related to thromboembolic event at 12 months, a sample size of 100 patients would provide >99% probability observing at least one event. However, if the event rate was 1%, it would still provide >63% probability of observing at least one event. While designed to evaluate 100 patients, the sample size was subsequently increased to 200 patients to meet FDA regulatory authority requests. For the primary endpoints and the secondary PTS endpoint at 6 and 12 months postenrollment, time-to-event analyses were summarized as Kaplan–Meier estimates, along with descriptive rates. Subgroup analyses included age strata and sex. For the descriptive analyses, patients with early withdrawal or who were lost to follow-up were deemed nonevents. Patients were censored from the survival analyses if they withdrew early, were lost to follow-up, or did not

have VTE or bleeding episodes. A sensitivity analysis was also conducted including all patients entered in the study and the full study period from entry until the day of the last follow-up visit, or until they were lost to follow-up, death, or consent was withdrawn ("on-treatment plus follow-up"). The pharmacokinetic/pharmacodynamic full analysis set consisted of all patients with ≥1 postbaseline measurement. Pharmacokinetic results were summarized descriptively. Pharmacokinetic/pharmacodynamic relationships were explored using graphical analyses. Safety and adverse events were summarized descriptively.

Results

Participants and follow-up

At European Union database lock in March 2019, 204 patients from 60 sites in 22 countries had entered the trial, with 1 adolescent not treated (due to inability to take treatment) (Figure 1). The median exposure to dabigatran was 36.3 (range 0-57) weeks. Risk factors resolved in 32 children during the trial, leading to treatment discontinuation. In 56/203 (27.6%) children, treatment was discontinued prematurely for the following reasons: target dabigatran concentration not achieved after one dose modification (n = 25), noncompliance with protocol (n = 4), VTE recurrence (n = 3; however, one of these VTE events was not confirmed to be a VTE recurrence by the adjudication committee and therefore was not included in the analysis), worsening of other pre-existing disease (n = 2), other adverse events (n = 4), consent withdrawn regarding dabigatran treatment (n = 2), and other (n = 16). The trial was discontinued prematurely (28-day follow-up period not completed as planned) in 24/203 (11.8%) children, with reasons being adverse events (n = 3), noncompliance with trial protocol (n = 2), consent withdrawn (n = 5), and other (n = 14). Only 4 patients discontinued both treatment and trial prematurely. All other patients who discontinued the trial prematurely completed the treatment period as planned, but discontinued the trial during the follow-up (posttreatment) period. Baseline demographics are shown in Table 1. Of the

203 treated children, 115 (56.7%) were children receiving chronic anticoagulation, who were newly exposed to dabigatran, and 88 (43.3%) were rolled over from the DIVERSITY trial (59 [29.1%] previously treated with dabigatran and 29 [14.3%] with SOC). No children required oral solution; 171/203 (84.2%) and 32/203 (15.8%) took capsules and pellets, respectively. Overall, 113/203 (55.7%) children were male, 101/203 (49.8%) were Central European, and 185/203 (91.1%) were white. Low molecular weight heparin was the most frequently used prior anticoagulant, prescribed for 152/203 (74.9%) children. Deep vein thrombosis other than central line related thrombosis and cerebral venous thrombosis was the most frequent VTE, reported in 154/203 (75.9%) of children and 35/203 (17.6%) children had PTS at baseline.

Information on previous VTE and baseline medical conditions with increased risk of thrombosis was available for 199 out of 203 patients. Prior confirmed VTE (before the index [most recent] VTE event in this trial) was reported by 36/199 (18.1%) children (range of 2-6 confirmed VTE events including the most recent event) (Table 2). Previous VTE was reported as being unprovoked in 25/36 (69.4%) and provoked in 13/36 (36.1%) children. There were 35 of 199 (17.6%) children who had PTS at baseline. The most common medical conditions with increased risk of thrombosis were congenital heart disease (12/199 [6.0%]), hematologic cancer (11/199 [5.5%]), and the presence of a central venous line or catheter (11/199 [5.5%]). Inherited thrombophilia was reported in 91/203 (44.8%) children; of these, the following disorders were reported: factor V Leiden mutation 34 (16.7%), prothrombin mutation 17 (8.4%), antithrombin deficiency 20 (9.9%), protein C/S deficiency 23 (11.3%), and other coagulation disorders 23 (11.3%). Of other conditions requiring secondary VTE prophylaxis, recurrent unprovoked VTE was the most common, reported for 29/203 (14.3%) children.

Primary endpoints

Overall, 2/203 (1.0%) children experienced recurrent VTE, one within 3 months of treatment and the other one within 6 months of treatment (Table 3 and Figure 2A). Both were female adolescents who had had deep vein thrombosis (n = 1) and pulmonary embolism (n = 1) as their most recent VTE event. Clinical risk factors that required secondary VTE protection were methylenetetrahydrofolate reductase (MTHFR) A1298C homozygous mutation in one female whose most recent VTE event was 3.5 months previously. In the other female, whose most recent VTE event was 26 months previously, they were MTHFR A1298C, plasminogen activator inhibitor-1 46156 heterozygote mutation, and protein S deficiency. The probability of freedom from recurrent VTE at 12 months across all age strata during the on-treatment period was 0.988 (95% confidence interval [CI], 0.951-0.997). Consistent results were observed for the full study period: on-treatment plus follow-up (probability of freedom from recurrent VTE at 12 months, 0.952; CI, 0.900-0.977).

The probability of freedom from bleeding at 12 months during the on-treatment period was 0.752 (95% CI, 0.672-0.815). Consistent results were observed for the full study period: on-treatment plus follow-up (probability of freedom from bleeding at 12 months, 0.771; CI, 0.699-0.827). Of the 40/203 (19.7%) children reporting bleeding events, 1.5% (3/203) were MBEs, 1.0% (2/203) were CRNM bleeding events, and 18.2% (37/203) were minor bleeding events (Table 3). The location of investigator-reported on-treatment bleeding events with dabigatran is shown in supplemental Table 2. Of the 3 children reporting MBEs, one was a 17-year-old female with an MBE originating from a venous varix in the right leg, and was treated with idarucizumab (Praxbind®) to reverse dabigatran in the context of a clinical trial (NCT02815670); one was a 16-year-old male who experienced an extrapleural hematoma following surgery, 3 days after a temporary interruption of dabigatran for planned surgery; and one was a 17-year-old male with thrombophilia and positive tests for homocysteinemia, high levels of lupus anticoagulant, and anti-cardiolipin antibodies who presented with an episode of hemoptysis and the treatment with dabigatran was switched to another anticoagulant. This patient experienced a pulmonary embolism with a fatal outcome 6 days

after stopping dabigatran treatment. For the 2 children reporting CRNMBEs, one was a 17-year-old male who experienced a cut in a finger that required medical/surgical intervention (stitches) to achieve hemostasis, and one was a 10-year-old female who presented with heavy menses after starting her menstrual cycle. There were no deaths while patients were on treatment.

Secondary endpoints

In total, PTS was newly reported in 2 adolescent males out of 162 patients (1.2%) who had DVT or central line thrombosis as their most recent VTE (Table 3 and Figure 2B)—one within 3 months and the other within 3-6 months of treatment. The probability of freedom from newly diagnosed PTS at 12 months across all age strata during the on-treatment period was 0.985 (95% CI, 0.939-0.996). Consistent results were observed for the full study period: on-treatment plus follow-up (probability of freedom from newly diagnosed PTS at 12 months, 0.980; 95% CI, 0.938-0.993). Clinical risk factors that required secondary VTE protection in these patients were i) factor V Leiden (heterozygous mutation) and prothrombin mutation (homozygous mutation) in one male whose most recent VTE event was 3 months previously (Modified Villalta score 2), and ii) factor V Leiden (heterozygous mutation), prothrombin (heterozygous mutation), and complete occlusion of the vena cava in one male whose most recent VTE event was 11.5 months previously (Modified Villalta score 3).

Adverse events were reported by 152/203 (74.9%) of children, with the most common being nasopharyngitis (34/203 [16.7%]), headache (33/203 [16.3%]), and abdominal pain (21/203 [10.3%]) (Table 4). Serious adverse events were experienced by 25/203 (12.3%) of children, and adverse events leading to treatment discontinuation were reported by 12/203 (5.9%) children.

At end of treatment, according to investigators, 124/126 (98.4%) and 16/17 (94.1%) children had good or satisfactory acceptance of capsules and pellets, respectively, and were able to take them very often or all of the time (124/126 [98.4%] and 16/17 [94.1%] for capsules and

pellets, respectively) (supplemental Table 3). Overall, dabigatran geometric mean (gCV%) trough exposure over all visits was 88.8 ng/mL (42.6); across age strata it was 96.5 ng/mL (34.8) for children aged 12 to <18 years (n = 153), 74.7 ng/mL (37.1) for those aged 2 to <12 years (n = 38), and 40.9 ng/mL (97.1) for those aged from >3 months to <2 years (n = 8) (supplemental Table 4). Pharmacokinetic/pharmacodynamic curves showed a linear relationship between total dabigatran plasma concentration and dTT and ECT, and a nonlinear relationship between total dabigatran plasma concentrations and activated partial thromboplastin time (Figure 3). During the on-treatment period, 26.1% of patients had a dose adjustment (increase or decrease of dose).

Discussion

This trial is the first to describe clinical outcomes in children aged <18 years being treated with dabigatran etexilate for secondary VTE prevention. We observed a low frequency of recurrent VTEs and few MBEs or CRNMBEs during dabigatran treatment in this setting. The rate of newly diagnosed PTS with dabigatran treatment in the study was 2/162 (1.2%). Using an age- and bodyweight-adjusted dosing algorithm, dabigatran plasma trough exposure was similar to that observed in adults.[16] In addition, the dabigatran pharmacokinetic/pharmacodynamic relationship seen in this pediatric population was similar to that seen in the adult setting.[23]

In terms of antithrombotic effect, the DIVERSITY trial has shown similar efficacy for dabigatran vs SOC when treating children aged <18 years with acute VTE, as well as the suitability of a pediatric dabigatran-dosing algorithm.[24] In that trial, there was a slightly higher frequency of recurrent VTE in children being treated with dabigatran for acute VTE (3.8%) than in this trial (1.0%).[24] This difference likely reflects the time since the index VTE event occurred, accompanied by a higher prothrombotic state during their acute VTE setting.

Our study population was comprised of approximately 20% of patients with the so-called high-risk inherited thrombophilia (protein S/C or antithrombin deficiency) and an additional 10% of patients with antiphospholipid syndrome (APS). In comparison, European investigators analysed a multicenter German–Israeli database to study the impact of genetically confirmed, high-risk, inherited thrombophilia on recurrent VTE in children and adults after cessation of anticoagulation.[25] A cumulative incidence of thrombosis recurrence of approximately 4% was observed at 12 months of follow up among pediatric patients.[25] A different analysis of the same database suggests these patients may have been off anticoagulation between 3 and 9 months after their event,[26] which could explain their higher frequency of thrombosis recurrence. Additionally, 2 pediatric studies on APS in patients with arterial and venous thrombosis reported recurrence of thrombosis rates of 19% and 29% with mean follow-up periods of 6.1 and 5.7 years, respectively.[27,28] While the follow-up duration of those studies was longer than in our study, and the participants of those may not match our study population, these comparisons contribute to placing the overall VTE recurrence rate reported herein in the context of the literature. To address the issue of lupus anticoagulants and direct oral anticoagulants (DOACs) in adult patients with high-risk, triple-positive APS, a lack of benefit and increased thrombotic risk has been reported following treatment with the direct factor Xa inhibitor rivaroxaban compared with warfarin,[29] raising the question of whether all DOACs should be avoided in this setting. However, as dabigatran has a different mode of action and directly inhibits thrombin, dabigatran might potentially lead to a more beneficial outcome in such patients. Indeed, a post-hoc pooled analysis of the RE-COVER/RE-COVER II and RE-MEDY trials found no significant differences in efficacy and safety between dabigatran and warfarin in adult patients with APS.[30] Of note, APS-positive patients comprised a small number of subjects enrolled (71 treated with dabigatran vs. 80 treated with warfarin), and a distinction between high risk or regular APS status was not included.[30] At present, prospective data regarding the efficacy and safety of dabigatran in the high-risk, triple-positive APS setting are lacking, and clinical trials are required.

Importantly, our trial results compare favorably to prior reports of VTE recurrence in the pediatric population. In the REVIVE trial, an open-label, pediatric, randomized, controlled study where the LMWH reviparin was compared to unfractionated heparin/VKA to treat VTE, the rate of venous thrombosis recurrence or death of patients treated with LMWH was 5.6%.[31] Similarly, a meta-analysis of LMWH pediatric studies reported pooled incidence rates for the development of recurrent VTE on LMWH secondary prophylaxis as being 5.2%,[32] while other LMWH pediatric dose-finding studies have reported VTE recurrence rates of 3%.[33]

In both trials, the frequency of any bleeding events on treatment with dabigatran was similar (19.7% in this trial and 19.9% in DIVERSITY), with a low incidence of MBEs in both studies (1.5% in this trial and 2.6% in DIVERSITY). Our bleeding complications align with results in the pediatric literature. The REVIVE trial with the LMWH reviparin reported a major bleeding rate of 5.6%.[31] Likewise, a meta-analysis of LMWH pediatric studies reported a pooled incidence rate for major bleeding of 1.8% and 6.5% for once-daily and twice-daily administration, respectively.[32]

In relation to newly diagnosed PTS, the incidence of 1.2% (all cases being possible mild ones) raises the concern as to whether these data were evaluated prematurely. Of note, the last official recommendation from the International Society on Thrombosis and Haemostasis Subcommittee stated that possible PTS should be detected after 6 months from the index limb deep vein thrombosis, and definitive PTS after 12 months.[34] Interestingly, almost 70% of the index VTEs were unprovoked, a known risk factor for PTS in children.[35,36] Furthermore, the baseline PTS detected for patients with previous VTE was 17%, which is lower than the weighted mean (43%, 95%CI, 38%-48%) reported for pediatric PTS detected retrospectively.[21] Contemporary work investigated if direct oral anticoagulants (ie, rivaroxaban) can reduce the rate of PTS in adults with limb deep vein thrombosis in comparison to LMWH/VKA by providing a more stable anticoagulation, but this protective effect was not initially confirmed (odds ratio [OR], 0.76; 95% confidence interval [CI], 0.51-

1.13).[37] Recently, this suspicion arose again in adults treated with rivaroxaban (OR, 0.5; 95% CI, 0.3-0.9: $P = 0.02$).[38] Our low PTS rate will need to be re-evaluated after a longer follow-up. In our trial, <75% of children experienced adverse events,12% reported serious adverse events, and <6% of children discontinued treatment because of an adverse event. These data are comparable to adult patients treated in the pivotal VTE trials of dabigatran, apixaban and rivaroxaban. In the RE-COVER, RE-MEDY and RE-SONATE trials, 66–71% of patients treated with dabigatran experienced adverse events, 7–16% reported serious adverse events, and 7–9% discontinued treatment because of an adverse event.[13,14] Similarly, in the AMPLIFY and EINSTEIN trials, 67–71% and 63% of patients treated with apixaban and rivaroxaban, respectively, experienced adverse events, 13–16% and 12% reported serious adverse events, and 6–8% and 5% discontinued treatment because of an adverse event.[39-41]

Finally, an analysis of dabigatran pharmacokinetic/pharmacodynamic data from previous pediatric and adult trials indicates that the most appropriate assays for dabigatran might be dTT and ECT,[42] which is further supported by data from this trial, as well as the DIVERSITY trial.[24] Developmental changes in the hemostatic system had little effect on dabigatran pharmacokinetic/pharmacodynamic relationships, with children aged <2 months being the possible exception.[42] A pharmacokinetic simulation analysis of dabigatran exposure in pediatric patients (data on-file) has indicated that the impact of dose adjustments on overall exposure is minimal. Therefore, it is considered appropriate to follow an age- and weight-adjusted dosing algorithm in pediatric patients without monitoring of dabigatran plasma levels.

Our trial did not have a comparator arm, yet the present safety data complement the dabigatran safety data from DIVERSITY that does have a comparator arm and showed similar efficacy and safety of dabigatran vs SOC in pediatric patients treated for acute VTE.[24] As mentioned above, the duration of follow-up in our trial from DVT diagnosis to time of PTS

assessment during the study was also variable, given the variability in lag time from VTE diagnosis to enrollment in this study of extended VTE treatment.

In view of the low patient numbers and different risk profile of patients in stratum 3 (age >3 months to <2 years), our data cannot be extrapolated with absolute confidence to younger patients. Based upon the inclusion criteria and the study population (i.e., >60% unprovoked VTE), our findings apply most directly to pediatric patients with unprovoked VTE and those who require extended anticoagulant therapy (i.e., beyond 3 months post-VTE diagnosis). A final limitation is the exclusion of patients with early withdrawal from the study medication due to failing to reach target dabigatran concentrations not included in the main analyses. However, the results of the sensitivity analyses that included all patients entered, and the full study period (on-treatment plus follow-up), were consistent with those of the primary analyses. Moreover, the comparison of baseline patient and thrombus characteristics between patients withdrawn due to failing to reach target dabigatran concentrations vs the retained population show that there are no statistical differences in the 2 groups (supplemental Table 5).

In conclusion, this trial has shown favorable safety of pediatric formulations of dabigatran for secondary prevention of VTE in children aged from >3 months to <18 years with persistent VTE risk factors.

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Authorship

Contribution: All authors have been involved in the design and execution of the trial. L.R.B., M.A., J.H., L.B., E.C., L.G.M., I.N., P.S., T.K., O.Z., I.T., M.S., F.H., Z.S., J.K., S.G., M.B., and M.L. have been responsible for editing the manuscript during development, and all authors approved the final draft.

Conflict-of-interest disclosure:

Leonardo R. Brandão is a member of a Pediatric Expert Working Group for Boehringer Ingelheim, and has received Advisory Board fees from Boehringer Ingelheim.

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Matteo Luciani is a member of a Pediatric Expert Working Group for Boehringer Ingelheim, and reports no disclosures.

Data sharing statement

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to all relevant material, including participant-level clinical study data, and relevant material as needed by them to fulfill their role and obligations as authors under the International Committee of Medical Journal Editors criteria. Furthermore, clinical study documents (eg, study report, study protocol, statistical analysis plan) and participant clinical study data are available to be shared after publication of the primary manuscript in a peer-reviewed journal and once regulatory activities are complete and other criteria met per

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Prior to providing access, documents will be examined, and, if necessary, redacted and the data will be de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants.
Clinical Study Reports and Related Clinical Documents can be requested via this link: https://trials.boehringer-ingelheim.com/trial_results/clinical_submission_documents.html. All such requests will be governed by a Document Sharing Agreement.
Bona fide, qualified scientific and medical researchers may request access to de-identified, analyzable participant clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and governed by a Data Sharing Agreement, data are shared in a secured data-access system for a limited period of 1 year, which may be extended upon request. Researchers should use https://clinicalstudydatarequest.com to request access to study data.

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References

1. Andrew M, David M, Adams M, et al. Venous thromboembolic complications (VTE) in children: first analyses of the Canadian Registry of VTE. *Blood*. 1994;83(5):1251-1257.
2. Kenet G, Kirkham F, Niederstadt T, et al. Risk factors for recurrent venous thromboembolism in the European collaborative paediatric database on cerebral venous thrombosis: a multicentre cohort study. *Lancet Neurol*. 2007;6(7):595-603.
3. Manco-Johnson MJ. How I treat venous thrombosis in children. *Blood*. 2006;107(1):21-29.
4. Nowak-Gottl U, Junker R, Kreuz W, et al. Risk of recurrent venous thrombosis in children with combined prothrombotic risk factors. *Blood*. 2001;97(4):858-862.
5. Monagle P, Chan AKC, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e737S-e801S.
6. Monagle P, Cuello CA, Augustine C, et al. American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism. *Blood Advances*. 2018;2(22):3292.
7. Chan AK, Monagle P. Updates in thrombosis in pediatrics: where are we after 20 years? *Hematology Am Soc Hematol Educ Program*. 2012;2012:439-443.
8. Polikoff LA, Faustino EVS. Venous thromboembolism in critically ill children. *Curr Opin Pediatr*. 2014;26(3):286-291.
9. Massicotte MP, Sofronas M, deVeber G. Difficulties in performing clinical trials of antithrombotic therapy in neonates and children. *Thromb Res*. 2006;118(1):153-163.
10. U S Food and Drug Administration. Guidance for industry and review staff: pediatric information incorporated into human prescription drug and biological products labeling. [Updated 2016 August 4].

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm341394.pdf. Accessed

11. European Medicines Agency. Clinical investigation of medicinal products in the paediatric population: note for guidance on clinical investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99). [Updated 2016 August 04]. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002926.pdf. Accessed
12. Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation*. 2014;129(7):764-772.
13. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009;361(24):2342-2352.
14. Schulman S, Kearon C, Kakkar AK, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med*. 2013;368(8):709-718.
15. Halton JM, Lehr T, Cronin L, et al. Safety, tolerability and clinical pharmacology of dabigatran etexilate in adolescents. An open-label phase IIa study. *Thromb Haemost*. 2016;116(3):461-471.
16. Halton JML, Albisetti M, Biss B, et al. Phase IIa study of dabigatran etexilate in children with venous thrombosis: pharmacokinetics, safety, and tolerability. *J Thromb Haemost*. 2017;15(11):2147-2157.
17. Halton JML, Picard AC, Harper R, et al. Pharmacokinetics, pharmacodynamics, safety and tolerability of dabigatran etexilate oral liquid formulation in infants with venous thromboembolism. *Thromb Haemost*. 2017;117(11):2168-2175.
18. Luciani M, Albisetti M, Biss B, et al. Phase 3, single-arm, multicenter study of dabigatran etexilate for secondary prevention of venous thromboembolism in children: rationale and design. *Res Pract Thromb Haemost*. 2018;2(3):580-590.
19. Hayton WL. Maturation and growth of renal function: dosing renally cleared drugs in children. *AAPS PharmSci*. 2000;2(1):E3.

20. Mitchell LG, Goldenberg NA, Male C, Kenet G, Monagle P, Nowak-Gottl U. Definition of clinical efficacy and safety outcomes for clinical trials in deep venous thrombosis and pulmonary embolism in children. *J Thromb Haemost*. 2011;9(9):1856-1858.

21. Goldenberg NA, Donadini MP, Kahn SR, et al. Post-thrombotic syndrome in children: a systematic review of frequency of occurrence, validity of outcome measures, and prognostic factors. *Haematologica*. 2010;95(11):1952-1959.

22. Soosainathan A, Moore HM, Gohel MS, Davies AH. Scoring systems for the post-thrombotic syndrome. *J Vasc Surg*. 2013;57(1):254-261.

23. Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. *Clin Pharmacokinet*. 2008;47(5):285-295.

24. Albisetti M, Brandão L, Bomgaars L, et al. Efficacy and safety of dabigatran etexilate for treatment of venous thromboembolism in paediatric patients - results of the DIVERSITY trial. Abstract number: OC 57.3. *Res Pract Thromb Haemost*. 2019;03(S1):139-140.

25. Bruwer G, Limperger V, Kenet G, et al. Impact of high risk thrombophilia status on recurrence among children and adults with VTE: an observational multicenter cohort study. *Blood Cells Mol Dis*. 2016;62:24-31.

26. Limperger V, Kenet G, Goldenberg NA, et al. Impact of high-risk thrombophilia status on recurrence among children with a first non-central-venous-catheter-associated VTE: an observational multicentre cohort study. *Br J Haematol*. 2016;175(1):133-140.

27. Avčin T, Cimaz R, Silverman ED, et al. Pediatric antiphospholipid syndrome: clinical and immunologic features of 121 patients in an international registry. *Pediatrics*. 2008;122(5):e1100-e1107.

28. Berkun Y, Padeh S, Barash J, et al. Antiphospholipid syndrome and recurrent thrombosis in children. *Arthritis Rheum*. 2006;55(6):850-855.

29. Pengo V, Denas G, Zoppellaro G, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. *Blood*. 2018;132(13):1365-1371.

30. Goldhaber SZ, Eriksson H, Kakkar A, et al. Efficacy of dabigatran versus warfarin in patients with acute venous thromboembolism in the presence of thrombophilia: Findings from RE-COVER(R), RE-COVER II, and RE-MEDY. *Vasc Med*. 2016;21(6):506-514.

31. Massicotte P, Julian JA, Gent M, et al. An open-label randomized controlled trial of low molecular weight heparin compared to heparin and coumadin for the treatment of venous thromboembolic events in children: the REVIVE trial. *Thromb Res*. 2003;109(2-3):85-92.

32. Bidlingmaier C, Kenet G, Kurnik K, et al. Safety and efficacy of low molecular weight heparins in children: a systematic review of the literature and meta-analysis of single-arm studies. *Semin Thromb Hemost*. 2011;37(7):814-825.

33. Musgrave KM, Webber K, Murphy P, Avery P, Biss TT. Evaluation of the age-dependent dosing recommendations for the administration of daily tinzaparin in children with thrombosis. *J Thromb Haemost*. 2017;15(12):2361-2366.

34. Goldenberg NA, Brandao L, Journeycake J, et al. Definition of post-thrombotic syndrome following lower extremity deep venous thrombosis and standardization of outcome measurement in pediatric clinical investigations. *J Thromb Haemost*. 2012;10(3):477-480.

35. Avila ML, Duan L, Cipolla A, et al. Postthrombotic syndrome following upper extremity deep vein thrombosis in children. *Blood*. 2014;124(7):1166-1173.

36. Avila ML, Pullenayegum E, Williams S, Yue N, Krol P, Brandao LR. Postthrombotic syndrome and other outcomes of lower extremity deep vein thrombosis in children. *Blood*. 2016;128(14):1862-1869.

37. Cheung YW, Middeldorp S, Prins MH, et al. Post-thrombotic syndrome in patients treated with rivaroxaban or enoxaparin/vitamin K antagonists for acute deep-vein thrombosis. A post-hoc analysis. *Thromb Haemost*. 2016;116(4):733-738.

38. Utne KK, Dahm A, Wik HS, Jelsness-Jorgensen LP, Sandset PM, Ghanima W. Rivaroxaban reduces the rate of post-thrombosis syndrome after DVT – a cross-

sectional study comparing rivaroxaban to warfarin. *J Thromb Haemost* 2017;1:1-15. Abstract OC 60.12.

39. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369(9):799-808.

40. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med*. 2013;368(8):699-708.

41. Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363(26):2499-2510.

42. Maas H, Gropper S, Huang F, et al. Anticoagulant Effects of Dabigatran in Paediatric Patients Compared with Adults: Combined Data from Three Paediatric Clinical Trials. *Thromb Haemost*. 2018;118(9):1625-1636.

TABLES

Table 1. Baseline patient demographics and characteristics by age strata

	Dabigatran			Total N = 203
	12 to <18 y n = 153	2 to <12 y n = 42	0 to <2 y n = 8	
Dabigatran formulation,* n (%)				
Capsules	153 (100.0)	18 (42.9)	0	171 (84.2)
Pellets	0	24 (57.1)	8 (100.0)	32 (15.8)
Age, y, mean (SD)	15.1 (1.6)	7.0 (3.0)	0.6 (0.5)	12.8 (4.5)
Male, n (%)	87 (56.9)	21 (50.0)	5 (62.5)	113 (55.7)
Region, n (%)				
Central/Eastern Europe	73 (47.7)	21 (50.0)	7 (87.5)	101 (49.8)
Western Europe	35 (22.9)	12 (28.6)	0	47 (23.2)
North America	37 (24.2)	5 (11.9)	1 (12.5)	43 (21.2)
Latin America	5 (3.3)	2 (4.8)	0	7 (3.4)
Asia	2 (1.3)	1 (2.4)	0	3 (1.5)
Israel	1 (0.7)	1 (2.4)	0	2 (1.0)
Race,† n (%)				
White	141 (92.2)	37 (88.1)	7 (87.5)	185 (91.1)
Asian	6 (3.9)	1 (2.4)	0	7 (3.4)
Black or African American	4 (2.6)	3 (7.1)	0	7 (3.4)
Multiple	1 (0.7)	1 (2.4)	1 (12.5)	3 (1.5)
Body mass index, kg/m^2, mean (SD)	24.7 (5.4)	17.8 (2.4)	16.1 (1.2)	22.9 (5.7)
eGFR,‡ mL/min/1.73 m^2, mean (SD)	101.3 (26.6)	128.5 (25.2)	125.6 (15.7)	107.8 (28.3)
Source of patients				
Chronically anticoagulated children newly exposed to dabigatran	82 (53.6)	26 (61.9)	7 (87.5)	115 (56.7)
Rollover patients treated with dabigatran in the DIVERSITY trial	46 (30.1)	12 (28.6)	1 (12.5)	59 (29.1)
Rollover patients treated with SOC in the DIVERSITY trial	25 (16.3)	4 (9.5)	0	29 (14.3)
Prior anticoagulation treatment,§ n (%)				
Low-molecular-weight heparin	116 (75.8)	29 (69.0)	7 (87.5)	152 (74.9)
Vitamin K antagonist	61 (39.9)	11 (26.2)	1 (12.5)	73 (36.0)
Unfractionated heparin	46 (30.1)	10 (23.8)	2 (25.0)	58 (28.6)
Direct oral anticoagulant‖	46 (30.1)	12 (28.6)	1 (12.5)	59 (29.1)
Fondaparinux	1 (0.7)	0	0	1 (0.5)
Other	14 (9.2)	1 (2.4)	0	15 (7.4)

Most recent venous thromboembolic event,¶ n (%)				
DVT (other than central line and cerebral venous thrombosis)	126 (82.4)	24 (57.1)	5 (62.5)	155 (76.4)
Pulmonary embolism	19 (12.4)	1 (2.4)	0	20 (9.9)
Central line thrombosis	2 (1.3)	3 (7.1)	2 (25.0)	7 (3.4)
Cerebral venous thrombosis and/or sinus thrombosis	8 (5.2)	14 (33.3)	1 (12.5)	23 (11.3)
DVT (other than central line and cerebral venous thrombosis) or central line thrombosis	128 (83.7)	27 (64.3)	7 (87.5)	162 (79.8)
Risk factors for venous thromboembolism, n (%)				
1 prespecified# risk factor	93 (60.8)	28 (66.7)	5 (62.5)	126 (62.1)
≥2 prespecified# risk factor	50 (32.7)	9 (21.4)	2 (25.0)	61 (30.0)
Other risk factors requiring further anticoagulation**	10 (6.5)	5 (11.9)	1 (12.5)	16 (7.9)

DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; SD, standard deviation; SOC, standard of care; VTE, venous thromboembolism.

*One adolescent was not treated.

†Missing data for one adolescent.

‡Calculated using the Schwartz formula.

§Nonanticoagulation therapy was used to treat the most recent VTE in 5 adolescents, 2 children aged 2 to <12 years, and one child aged from >3 months to <2 years.

‖Rollover patients treated with dabigatran in the DIVERSITY trial

¶Patients could be assessed with more than one type of most recent VTE.

#Defined as inherited thrombophilia, short bowel syndrome, congenital nephrotic syndrome, inflammatory bowel disease, recent immobilization, presence of central venous/arterial line or catheter, total parental nutrition, systemic lupus erythematosus, systemic sclerosis or inflammatory vasculopathies, recurrent idiopathic (unprovoked) VTE, structural venous abnormality, antiphospholipid and/or lupus antibodies.

**As assessed by investigators, not within prespecified categories of risk factors.

Table 2. Baseline risk factors for VTE by age strata

	Dabigatran			Total
	12 to <18 y	2 to <12 y	0 to <2 y	
Medical history of previous thromboembolic events	**n = 150**	**n = 41**	**n = 8**	**N = 199***
History of prior VTE event (before the index VTE event in this trial), n (%)				
Yes	28 (18.7)	6 (14.6)	2 (25.0)	36 (18.1)
Number of prior confirmed VTE events†				
2	9 (6.0)	1 (2.4)	0	10 (5.0)
3	13 (8.7)	4 (9.8)	1 (12.5)	18 (9.0)
4	4 (2.7)	0	0	4 (2.0)
5	1 (0.7)	0	0	1 (0.5)
6	1 (0.7)	1 (2.4)	1 (12.5)	3 (1.5)
No	122 (81.3)	35 (85.4)	6 (75.0)	163 (81.9)
Previous VTE,‡ n (%)	**n = 28**	**n = 6**	**n = 2**	**n = 36**
Unprovoked	21 (75.0)	3 (50.0)	1 (50.0)	25 (69.4)
Provoked	7 (25.0)	4 (66.7)	2 (100.0)	13 (36.1)
Postthrombotic syndrome,§ n (%)	29 (19.3)	5 (12.2)	1 (12.5)	35 (17.6)
Medical conditions/circumstances with increased risk of thrombosis, n (%)	**n = 150**	**n = 41**	**n = 8**	**N = 199***
Congenital heart disease	6 (4.0)	3 (7.3)	3 (37.5)	12 (6.0)
Hematologic cancer	4 (2.7)	7 (17.1)	0	11 (5.5)
Presence of central venous line	3 (2.0)	4 (9.8)	4 (50.0)	11 (5.5)
Recent immobilization‖	7 (4.7)	0	0	7 (3.5)
Any history of solid cancer	1 (0.7)	2 (4.9)	1 (12.5)	4 (2.0)
Presence of other venous or arterial catheter	2 (1.3)	1 (2.4)	0	3 (1.5)
Hypertension	3 (2.0)	0	0	3 (1.5)
Heart failure	0	1 (2.4)	1 (12.5)	2 (1.0)
History of stroke or transient ischemic attack	0	1 (2.4)	0	1 (0.5)
Liver disease (currently not active)	0	0	1 (12.5)	1 (0.5)
History of major or clinically relevant bleeding event	0	1 (2.4)	0	1 (0.5)
Total parenteral nutrition−dependency	1 (0.7)	0	0	1 (0.5)
Clinical risk factors requiring secondary VTE prevention, n (%)	**n = 153**	**n = 42**	**n = 8**	**N = 203**
Inherited thrombophilia¶,#	79 (51.6)	11 (26.2)	1 (12.5)	91 (44.8)
Factor V Leiden mutation**	32 (20.9)	2 (4.8)	0	34 (16.7)
Prothrombin mutation††	15 (9.8)	2 (4.8)	0	17 (8.4)
Antithrombin deficiency	16 (10.5)	4 (9.5)	0	20 (9.9)
Protein S/C deficiency	19 (12.4)	4 (9.5)	0	23 (11.3)
Other‡‡	20 (13.1)	2 (4.8)	1 (12.5)	23 (11.3)
2 or more thrombophilia conditions	26 (17.0)	4 (9.5)	0	30 (14.8)
Congenital nephrotic syndrome	0	1 (2.4)	0	1 (0.5)

Other conditions requiring secondary VTE prophylaxis, n (%)	n = 153	n = 42	n = 8	N = 203
Antiphospholipid antibodies and/or lupus antibodies	18 (11.8)	1 (2.4)	1 (12.5)	20 (9.9)
Recurrent unprovoked VTE	21 (13.7)	7 (16.7)	1 (12.5)	29 (14.3)
Structural venous abnormality§§	20 (13.1)	6 (14.3)	0	26 (12.8)
Any other risk factor requiring secondary prophylaxis	47 (30.7)	18 (42.9)	6 (75.0)	71 (35.0)

CRF, clinical report form; GP, glycoprotein; MTHFR, methylenetetrahydrofolate reductase; MTRR, methionine synthase reductase; PAI, plasminogen activator inhibitor; VTE, venous thromboembolism.

*Medical history of previous VTE was collected starting CRF Version 2; missing data for 4 children who were assessed with CRF Version 1.

†Includes the most recent VTE event.

‡Children may be counted in >1 category. Percentages based on the number of patients with a history of prior VTE events. Missing data for 163 children.

§Missing data for one adolescent.

‖Illness requiring bed rest or involving paralysis.

¶The number of children with ≥1 of the conditions listed.

#Missing data for 2 adolescents and 2 children ages 2 to <12 years.

**Gln506 (rs6025), hetero- or homozygous.

††G20210A mutation.

‡‡Other coagulation disorders/thrombophilias including: MTHFR mutation, MTRR mutation, PAI 4G/5G polymorphism, factor XII deficiency, integrin A2 mutation, hyperhomocysteinemia, fibrinogen mutation, GP IA mutation, GP IIIA mutation, factor VIII elevation.

§§Structurally abnormal venous system, eg, inferior vena cava malformation, Paget-Schroetter disease (thoracic outlet syndrome), May-Thurner syndrome (iliac vein compression syndrome).

Table 3. On-treatment VTEs, postthrombotic syndrome, bleeding events, and fatal events at 12 months by age strata (treated set)

	Dabigatran			Total N = 203
	12 to <18 y n = 153	2 to <12 y n = 42	0 to <2 y n = 8	
Recurrent VTE event, n (%)	2 (1.3)	0	0	2 (1.0)
Subgroup analysis,* n/N (%)				
Sex				
Male	0/87 (0.0)	0/21 (0.0)	0/5 (0.0)	0/113 (0.0)
Female	2/66 (3.0)	0/21 (0.0)	0/3 (0.0)	2/90 (2.2)
Postthrombotic syndrome,† n (%)	2/128 (1.6)	0/27 (0.0)	0/7 (0.0)	2/162 (1.2)
Subgroup analysis,* n/N (%)				
Sex				
Male	2/80 (2.5)	0/12 (0.0)	0/5 (0.0)	2/97 (2.1)
Female	0/48 (0.0)	0/15 (0.0)	0/2 (0.0)	0/65 (0.0)
Bleeding events, n (%)	37 (24.2)	2 (4.8)	1 (12.5)	40 (19.7)
Major	3 (2.0)	0	0	3 (1.5)
Clinically relevant non-major	1 (0.7)	1 (2.4)	0	2 (1.0)
Minor	34 (22.2)	2 (4.8)	1 (12.5)	37 (18.2)
All-cause death, n (%)	0	0	0	0

VTE, venous thromboembolism.

*Missing data for one adolescent.

†Calculated over the number of patients with DVT (other than central line and cerebral venous thrombosis) or central line thrombosis.

Table 4. Summary of adverse events, and adverse events occurring in ≥5% of children in either treatment group (treated set)

All data are n (%)	Dabigatran			Total
	12 to <18 y n = 153	2 to <12 y n = 42	0 to <2 y n = 8	N = 203
Children with any adverse event	120 (78.4)	25 (59.5)	7 (87.5)	152 (74.9)
Drug-related adverse event*	37 (24.2)	5 (11.9)	1 (12.5)	43 (21.2)
Children with serious adverse events†	19 (12.4)	6 (14.3)	0	25 (12.3)
Leading to death	0	0	0	0
Life-threatening	2 (1.3)	0	0	2 (1.0)
Requiring hospitalization	17 (11.1)	6 (14.3)	0	23 (11.3)
Prolonging hospitalization	1 (0.7)	1 (2.4)	0	2 (1.0)
Other	2 (1.3)	2 (4.8)	0	4 (2.0)
Children with adverse events of special interest‡	0	0	0	0
Children with adverse events leading to treatment discontinuation	9 (5.9)	2 (4.8)	1 (12.5)	12 (5.9)
Adverse events in ≥5% of children overall				
Nasopharyngitis	26 (17.0)	7 (16.7)	1 (12.5)	34 (16.7)
Drug-related	0	0	0	0
Serious adverse event	0	0	0	0
Headache	27 (17.6)	6 (14.3)	0	33 (16.3)
Drug-related	2 (1.3)	1 (2.4)	0	3 (1.5)
Serious	0	1 (2.4)	0	1 (0.5)
Abdominal pain§	19 (12.4)	2 (4.8)	0	21 (10.3)
Drug-related	5 (3.3)	2 (4.8)	0	7 (3.4)
Serious	1 (0.7)	0	0	1 (0.5)
Respiratory tract infection‖	15 (9.8)	3 (7.1)	0	18 (8.9)
Drug-related	0	0	0	0

Serious	1 (0.7)	0	0	1 (0.5)
Nausea	13 (8.5)	3 (7.1)	0	16 (7.9)
Drug-related	5 (3.3)	2 (4.8)	0	7 (3.4)
Serious	0	0	0	0
Vomiting	10 (6.5)	4 (9.5)	0	14 (6.9)
Drug-related	1 (0.7)	1 (2.4)	0	2 (1.0)
Serious	0	0	0	0
Cough	9 (5.9)	4 (9.5)	1 (12.5)	14 (6.9)
Drug-related	0	0	0	0
Serious	0	0	0	0
Dyspepsia	13 (8.5)	0	0	13 (6.4)
Drug-related	9 (5.9)	0	0	9 (4.4)
Serious	0	0	0	0
Pyrexia	11 (7.2)	2 (4.8)	0	13 (6.4)
Drug-related	0	0	0	0
Serious	0	0	0	0
Diarrhea	12 (7.8)	1 (2.4)	0	13 (6.4)
Drug-related	2 (1.3)	0	0	2 (1.0)
Serious	0	0	0	0
Pain in extremity	11 (7.2)	2 (4.8)	0	13 (6.4)
Drug-related	0	0	0	0
Serious	1 (0.7)	0	0	1 (0.5)
Epistaxis	10 (6.5)	1 (2.4)	1 (12.5)	12 (5.9)
Drug-related	5 (3.3)	1 (2.4)	1 (12.5)	7 (3.4)
Serious	0	0	0	0

*Investigator-defined.

†A child could be counted in >1 category.

‡Protocol-defined adverse events of special interest were elevated aspartate aminotransferase and/or alanine aminotransferase >3-fold upper limit of normal combined with an elevation of total bilirubin >2-fold upper limit of normal measured in the same blood draw sample, and a ≥2-fold increase in creatinine from baseline levels that is above the upper limit of normal.

§Includes children with upper abdominal pain.

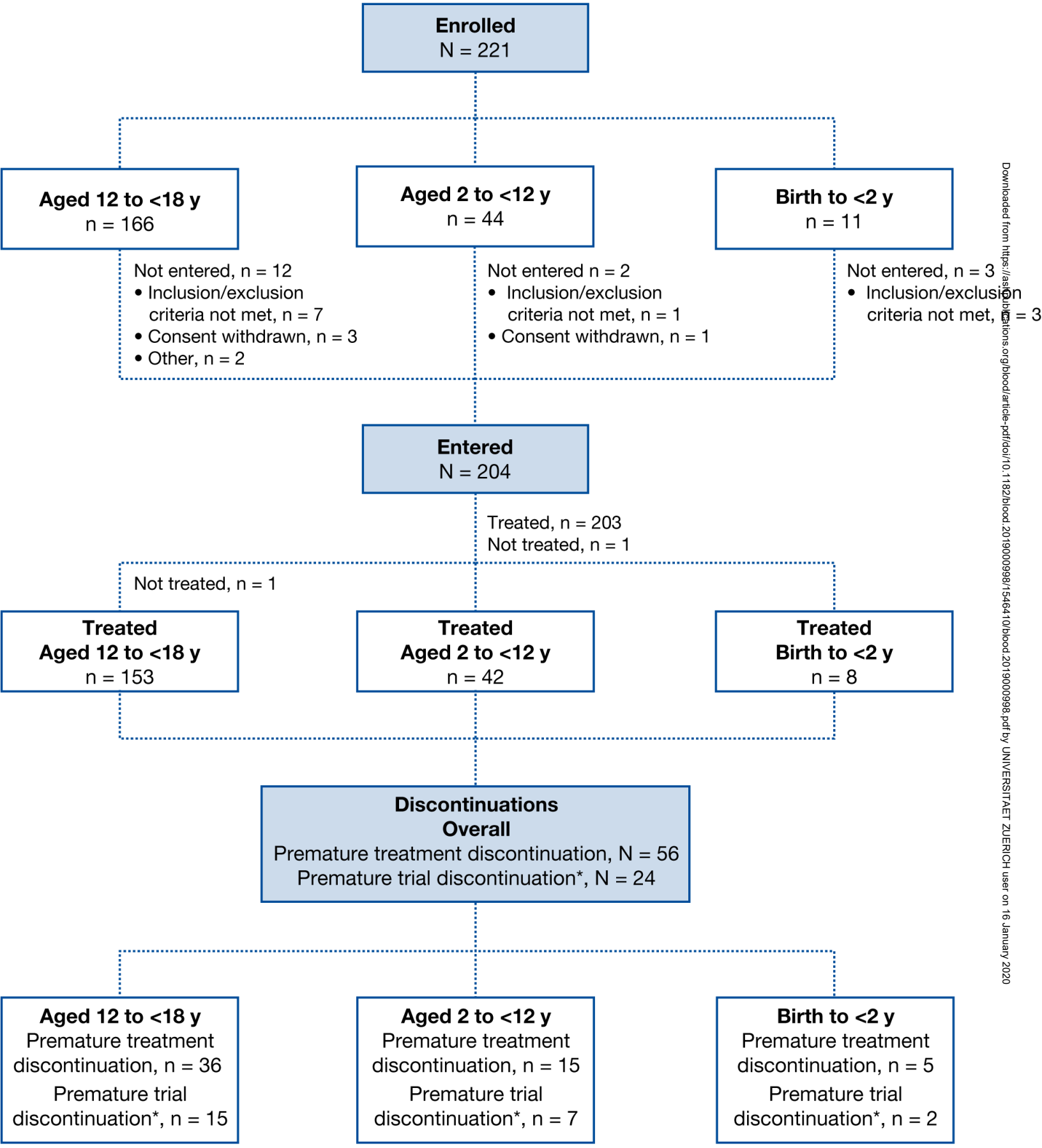
‖Includes children with upper respiratory tract infection and viral upper respiratory tract infection.

<FIGURE LEGENDS>

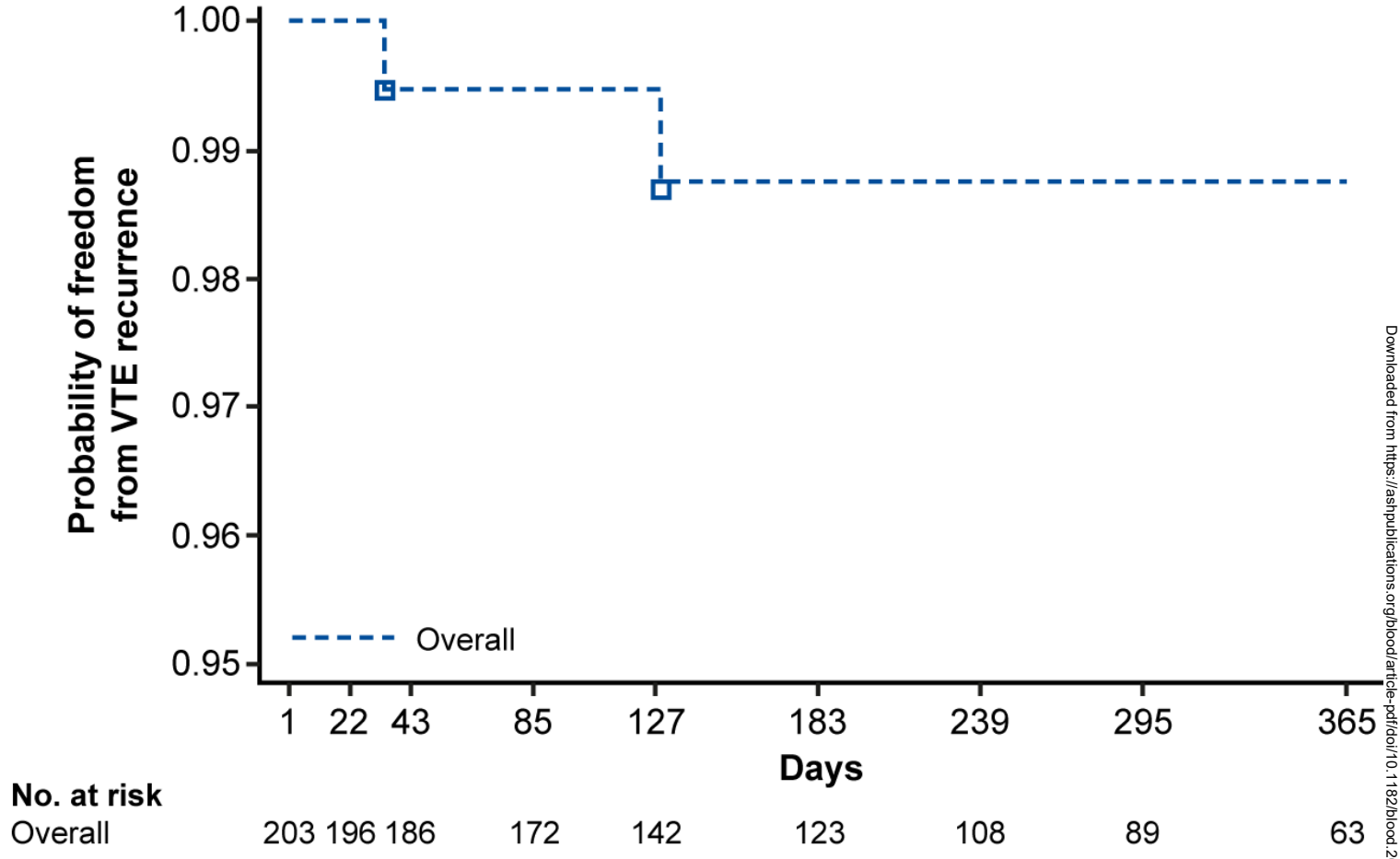
Figure 1. Disposition of patients.

Figure 2. Kaplan–Meier curves for all age strata combined (on-treatment) for time to (A) recurrent VTE and (B) postthrombotic syndrome (adjudicated data from the treated set). VTE, venous thromboembolism.

Figure 3. PK–PD relationship curves at trough sampling times for dabigatran PK and dTT (A, overall; B, aged 12 to <18 years; C, aged 2 to <12 years; D, aged from >3 months to <2 years), aPTT (E, overall; F, aged 12 to <18 years; G, aged 2 to <12 years; H, aged from >3 months to <2 years), and ECT (I, overall; J, aged 12 to <18 years; K, aged 2 to <12 years; L, aged from >3 months to <2 years) by age group. aPTT, activated partial thrombin time; Dabititrn, dabigatran titration; dTT, diluted thrombin time; ECT; ecarin clotting time; PD, pharmacodynamic; PK, pharmacokinetic.

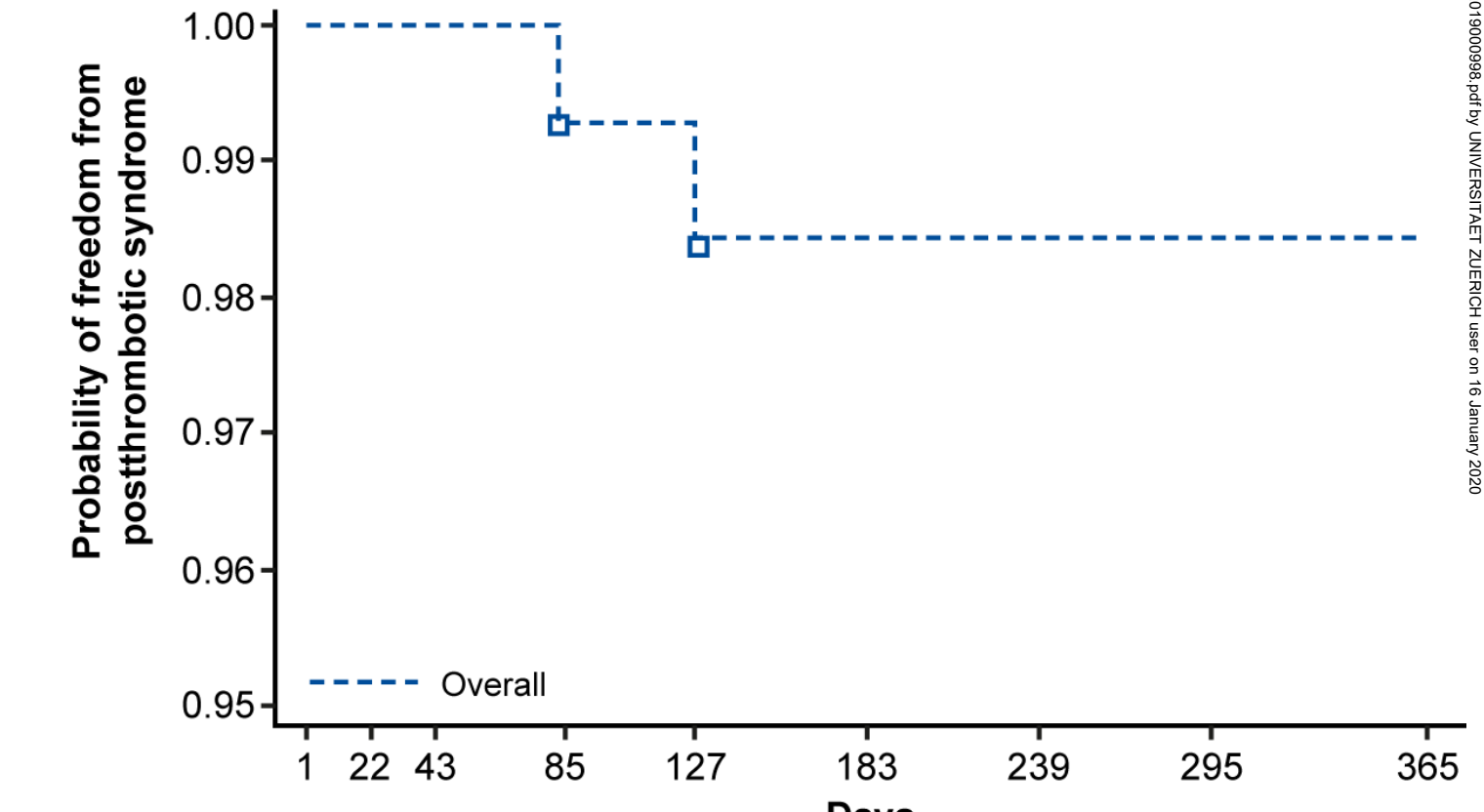


A



No. at risk									
Overall	203	196	186	172	142	123	108	89	63

B



No. at risk									
Overall	162	158	152	140	119	106	95	78	58